

Abnormal chromosome complement resulting from a familial inversion of chromosome 2

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SUMMARY It has been suggested that pericentric inversions of chromosome 2 increase the risk for spontaneous abortion but do not increase the risk for unbalanced recombinant offspring. We report our experience of a familial pericentric inversion of chromosome 2 resulting in two unbalanced recombinant offspring. Both subjects have 46,XX,rec(2),dup q,inv(2)(p25q35).

Pericentric inversions of chromosome 2 have been described in normal subjects, in association with mental retardation or congenital malformations or

both, and in patients with reproductive failure. Dutrillaux *et al*¹ report that inversions of chromosome 2 are not distributed at random, and should have an observed frequency below 0.05%. Djalali *et al*² estimate the incidence of pericentric inversions of chromosome 2 in the population to be 0.001% to 0.013%.

A recent review of published reports has failed to find carriers of a pericentric inversion of chromosome 2 with unbalanced recombinant offspring. We report our experience with two related subjects with identical karyotypes, 46,XX,inv(2)(p25q35). The offspring of both these women have an unbalanced recombinant 46,XX,rec(2),dup q,inv(2)(p25q35), which results in a deletion of bands 2p25→pter and duplication of bands 2q35→qter.



FIG 1 Patient 1 (IV.1) at four years three months.

Case reports

Patient 1 was originally seen because of failure to thrive. She was born at 44 weeks' gestation after an uncomplicated pregnancy to a 25 year old, gravida 1, para 0 female and her 34 year old husband. There was no known exposure to alcohol, drugs, or tobacco during the pregnancy. Delivery was vaginal with vertex presentation; birth weight was 3459 g and length 53 cm. There was meconium staining of the amniotic fluid at birth. Poor sucking was obvious during the newborn period. Developmentally, there was evidence of gross motor, fine motor, and language delay.

On examination at three months of age, head circumference was 35.9 cm (<2nd centile), length 62 cm (97th centile), weight 6.04 kg (75th centile), outer canthal distance 6 cm (20th centile), inner canthal distance 2.3 cm (50th centile), and interpupillary distance 4.3 cm (60th centile). The ears were mildly low set with posterior rotation and a simple helix. The nose had a broad root with a small upturned tip.

When examined at four years three months of age (fig 1), head circumference was on the 25th centile, height on the 50th centile, and weight on the 25th to 50th centile. There was obvious brachycephaly with skull asymmetry, the right part of the occiput being more prominent than the left. Hair patterning was unremarkable. Palpebral fissures were upward slanting with mild epicanthic folds. The ears were normally placed with a prominent antehelix and a

small sebaceous lump in front of the left ear. The nose had a broad root, bulbous bridge and tip, and small anteverted nares. The philtrum was prominent and long. The mouth had a thin vermilion border. The palate was high and narrow. There was microdontia and malar hypoplasia with mild micrognathia. Examination of the hands showed bilateral fifth finger clinodactyly, tapering fingers with absent creases over the distal interphalangeal joints, normal palmar flexion creases, and unremarkable dermatoglyphics. The finger pads were hypoplastic. The rest of the examination was within normal limits.

Patient 2 is the maternal aunt of patient 1. She was born at 43 weeks' gestation to healthy, non-consanguineous parents. The pregnancy had been uncomplicated apart from hyperemesis gravidarum. There was no history of prenatal exposure to drugs, alcohol, or tobacco. Delivery was vaginal with vertex presentation; birth weight was 3288 g. At birth, there was aspiration of amniotic fluid.

Developmentally, there was mild delay in acquisition of all skills with more severe delay in language development than in gross motor skills. She received special education from grade 5 onwards. IQ assessed at the age of 25 showed a verbal score of 78 with a performance score of 59 and a full scale score of 68. She is currently working at a Goodwill Sheltered Workshop.

She had frequent urinary tract infections from four months of age, and was subsequently found to have bladder neck obstruction, producing unilateral renal damage that required a right nephrectomy at



FIG 2 Patient 2 (III.1) at 32 years.

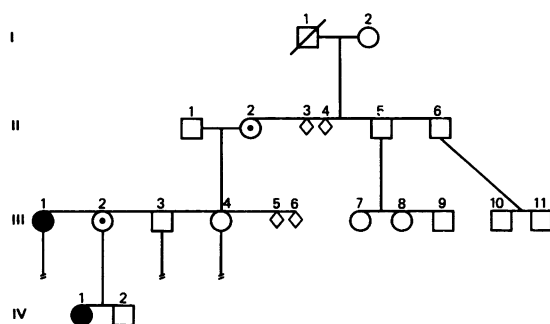


FIG 3 Family pedigree.

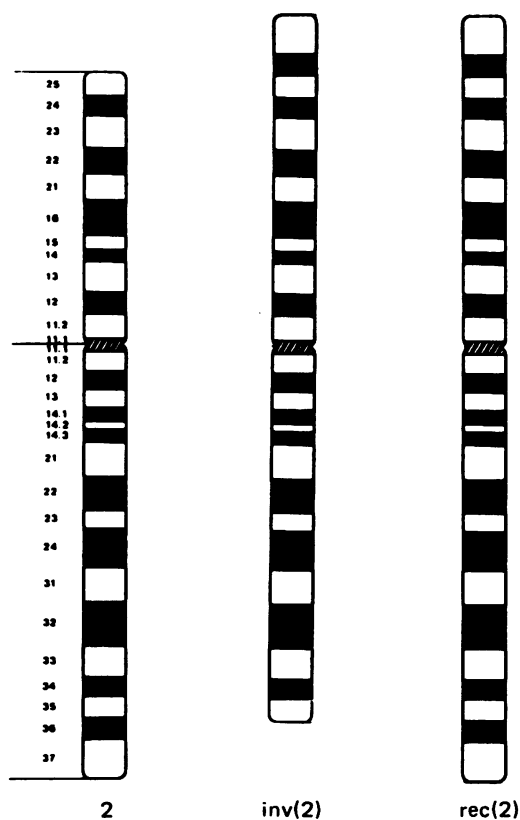


FIG 4 400 band stage ideograms of a normal chromosome 2, the inverted chromosome 2 seen in both parents, and the recombinant chromosome 2 seen in both patients.

two years of age. There is some residual impairment of left renal function. A coincidental accident at the age of nine has left her paraparetic and wheelchair bound.

On examination at the age of 32 (fig 2), head circumference was on the 2nd centile. The forehead was tall. The eyes were widely spaced with esotropia and prominent brows. The ears had an outfolded helix and prominent antehelix. The nose had a narrow bridge, sharp tip, and underhanging columella. The philtrum was long and poorly formed with a thin vermillion border to the lips. The palate was narrow with dental crowding. There was flattening of the mid face and a small chin. Examination of the hands showed short, wide distal phalanges and nails, with limited extension at the distal interphalangeal joints and metacarpophalangeal joints. Palmar flexion creases and dermatoglyphics were unremarkable. There was thoracic scoliosis.

A detailed pedigree (fig 3) shows that I.2 and II.2 had two miscarriages. There are no other family members with birth defects or intellectual impairment.

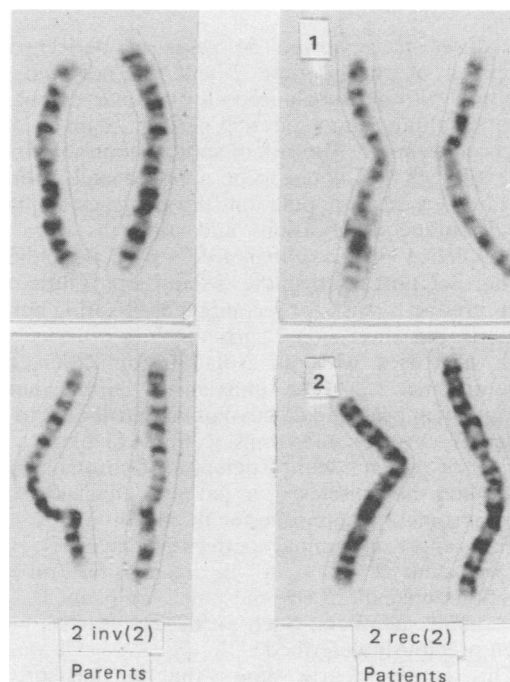


FIG 5 G banded chromosome 2 homologues of patients 1 and 2 and their parents. In each chromosome pair the abnormal chromosome 2 is on the right.

CYTOGENETIC STUDIES

Chromosome studies on both patients and their parents were performed on blood lymphocytes stimulated with phytohaemagglutinin. The cells were cultured for 72 hours at 37°C in 5% CO₂ in air. The medium (RPMI 1640) was supplemented with 25% fetal calf serum and 1% glutamine. Metaphase and prometaphase chromosomes were prepared at the 375 to 550 band stage by routine methods. Cells were harvested by standard methods and trypsin G (GTG) banded.

Initial chromosome analysis in both patients showed additional chromosomal material on the distal short arm of chromosome 2. Parental chromosome studies in both cases showed normal paternal chromosome complements and maternal karyotypes with a pericentric inversion of chromosome 2: 46,XX,inv(2)(p25q35). The karyotypes of both patients can therefore be designated 46,XX,rec(2)dup q,inv(2)(p25q35) (figs 4 and 5). This recombinant chromosome 2 is thought to be derived from a meiotic crossover in both inversion carrier mothers. This recombinant results in a deletion of the region 2p25→pter and duplication of the region 2q35→qter.

Discussion

Djalali *et al*² reviewed 54 cases of pericentric inversion of chromosome 2 and did not find a liveborn with an unbalanced chromosome complement resulting from a parental pericentric inversion of chromosome 2. The risk of spontaneous abortion and stillbirth was noted to be approximately twice that in the general population. It was suggested that the spontaneous abortions and stillbirths were a consequence of the unbalanced products. Other authors support the hypothesis that there is little or no reproductive risk for recombinant offspring born to pericentric inversion 2 carriers.²⁻⁷

In all cases with an isolated duplication of chromosome 2,⁸⁻¹⁸ the unbalanced chromosome complement occurred de novo or was attributed to a parental chromosome translocation. Similarly, a review of patients with a deletion of chromosome 2¹⁹⁻²¹ has not disclosed a parental inversion of chromosome 2 responsible for the deletion.

We report a familial pericentric inversion of chromosome 2 found to be responsible for a deletion/duplication chromosome complement in two family members. Such an occurrence has not been previously described.

This family clearly shows that carriers of a pericentric inversion of chromosome 2 have an increased risk for a liveborn child with an unbalanced chromosome complement, in addition to an increased

risk for spontaneous abortion or stillbirth. Because the pericentric inversion involves a large segment of chromosome 2, recombination through crossover events has resulted in deletion and duplication of small segments of chromosome 2. This could account for the viability of the offspring.

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Partial monosomy 3q in a boy with short stature, developmental delay, and mild dysmorphic features

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SUMMARY We describe the clinical and cytogenetic findings in a boy with an unbalanced karyotype involving monosomy for 3q27-q29. He does not resemble other reported cases of del(3q). Deletions of the long arm of chromosome 3 are extremely rare, having been reported in five cases, only two of which had terminal 3q deletions.

healthy, non-consanguineous parents. The family history was negative and there is a healthy brother and sister. The pregnancy was uneventful and the child was born at term after a normal delivery, weighing 2610 g. He was a floppy baby and subsequent development was slow; he first walked at two and a half years.

He was referred to the Genetics Clinic at eight years of age for assessment. At this stage his length

Case report

The proband, an eight year old male, was born to



FIG 1 Facial appearance of the proband at eight years.

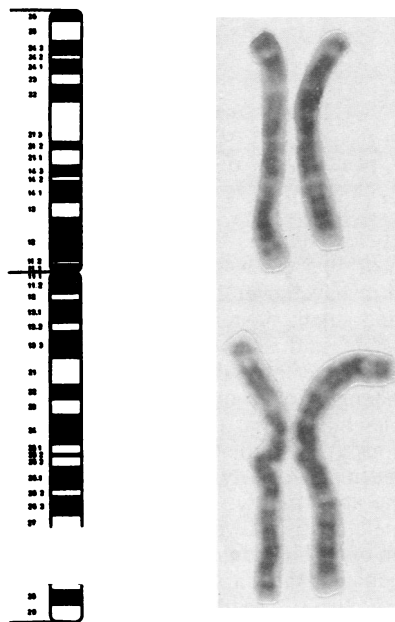


FIG 2 G banded partial karyotypes of the proband with the deleted chromosome on the right. The idiogram of chromosome 3 illustrates the breakpoint at 3q27.